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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
MEHTA, ASHWIN D

ART UNIT	PAPER NUMBER
1638	

DATE MAILED: 03/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,054	LAM, ERIC	
	Examiner	Art Unit	
	Ashwin Mehta	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The objection to the priority statement on page 1 of the specification is withdrawn, in light of its amendment.

3. The objections to claims 25, 29, and 30 are withdrawn in light of the claim amendments.

4. The rejection of claims 1-32 under 35 U.S.C. 112, 2nd paragraph is withdrawn, in light of the claim amendments.

5. The rejection of claims 1-23 under 35 U.S.C. 103(a) is withdrawn, and replaced with the rejection below.

Claim Rejections - 35 USC § 112

6. Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1: the recitation, "heterologous DNA segments" in line 4 renders the claim indefinite. It is unclear whether more than one segment is intended to be present in the DNA

construct. The specification does not discuss constructs that include multiple heterologous DNA segments. Further, in the paper submitted December 9, 2004, in response to an indefinite rejection of claim 1, Applicant indicates that "claim 1 has been amended to indicate that the heterologous DNA segment comprises the components listed in part a) and b)" (emphasis added, page 13, 2nd full paragraph). It is suggested that the recitation be replaced with --a heterologous DNA segment--.

7. Claims 24-32 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a DNA construct for integration of heterologous DNA segment into genomes, wherein the DNA construct is adapted for integrating a heterologous DNA segment at a pre-determined location in the Chlamydomonas genome, and a method for inserting a heterologous DNA molecule into a pre-determined location of a Chlamydomonas genome, does not reasonably provide enablement for DNA constructs adapted for integrating a heterologous DNA segment into pre-determined locations of other plant genomes, or methods for inserting a heterologous DNA into a pre-determined location in other plant genomes, or a method of activation tagging of a plant genome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims, for the reasons of record stated in the Office action mailed September 10, 2004. Applicant traverses the rejection in the paper filed December 9, 2004. Applicant's arguments were fully considered but were not found persuasive.

Applicant argues Puchta teaches that while the frequency of gene targeting in plants is low compared to mammals, that several instances of gene targeting in flowering plants has been

reported (response, page 15, 1st full paragraph). However, Puchta discusses how this frequency in plants is low enough that gene targeting is not feasible, which indicates that such techniques were not known in the prior art. Applicant argues that Puchta teaches that there is efficient gene targeting in Physcomitrella patens, a moss (response, page 15, 1st full paragraph). However, this is not representative of all plants. Applicant argues that Terada et al. discuss two reports of gene targeting in Arabidopsis, and teach a method for homologous recombination in rice (response, page 15, 1st full paragraph). However, as pointed out by Applicant, Terada et al. discuss flaws in the two reports concerning Arabidopsis. Further, as Terada et al. was published after the filing of the instant application, it cannot be relied on for fulfilling the enablement requirement. See *In re Glass*, 492 F.2d 1228, 181 USPQ 31 (CCPA 1974).

Applicant cites MPEP 2164.02 for teaching that an invention need not be actually reduced to practice if the invention is disclosed in such a manner as to enable one skilled in the art to practice it without undue experimentation. Applicant argues that the specification as a whole provides sufficient guidance, and that methods needed to practice the invention were known in the art, as supposedly evidenced by Miao et al. and Puchta (response, page 15, 2nd full paragraph and the paragraph bridging pages 15-16). However, the specification only provides prophetic direction, and does not provide any direction in overcoming the problems of the art at the time of filing. Miao et al. and Puchta do not teach methods to practice the invention with all species. Puchta only indicates that homologous recombination methods are known for P. patens and Chlamydomonas. These two plant species do not represent any other plant species, as Puchta and Terada et al. discuss the lack of success of gene targeting by homologous recombination in the prior art. Applicants argue that the lack of validation of the experiments of

Miao et al. does not indicate that the methods are invalid, but only that similar experiments have not been published (response, paragraph bridging pages 15-16). However, Puchta teaches that in Miao et al., the single recovered callus was a chimera for the targeted locus and could not be regenerated (page 174).

Applicants also again argue that Puchta teaches that there were several instances of gene targeting in flowering plants, but that the frequency was low, and that screening of a large number of plants is not undue experimentation (response, page 16, 2nd full paragraph). However, as discussed, Puchta et al. teach that the reports of gene targeting in Arabidopsis are not repeatable, and that the method of Miao et al. results in non-regenerable calli, and that "Time will tell when and by which approach gene targeting in higher plants will be achieved in a feasible way" (page 180).

Applicant cites MPEP 2164.05(a) for teaching that an Examiner should not rely on post-filing art to demonstrate non-enablement, except if the reference provides evidence of what one skilled in the art would have known on or before the effective filing date. Applicant argues that Terada et al. was improperly used to suggest the disclosure is non-enabling (response, paragraph bridging pages 16-17 and page 17, 1st full paragraph). However, MPEP 2164.05(a) also teaches that if individuals of skill in the art state that a particular invention is not possible after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing. Terada et al. teach the problems of reports concerning homologous recombination in the prior art, as discussed previously. Applicant also argues that the submission of Terada et al. to Nature Biotechnology at the time of filing and its publication four months after the filing date confirms that homologous recombination occurs in plants and that the level of skill in the art was high

(response, page 17, 1st full paragraph). However, publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. See MPEP 2164.05(a); *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976).

Regarding claim 29, Applicant argues that there may be multiple and single insertion events, that the claim is not limited to single insertion events, and that a pleiotropic effect may be required to achieve a desired phenotype (response, page 17, 1st full paragraph). However, it is unpredictable what the effect on the plant would be is numerous genes that would normally be dormant, suddenly become activated. Further, as the transposase is still active in such plants, the DNA segments would still be mobile. Applicants also argue that use of the construct of claim 24 in the method of claim 29 would be useful in altering the regulation of a specific gene, that replacement of an inducible promoter with a constitutive or tissue-specific promoter would have a profound effect on expression of the coding region (response, paragraph bridging pages 17-18). However, the specification does not teach what such profound effects are, or how one skilled in the art would use such plants, if they are even viable. It is also noted that Applicants state that claim 29 does not read on random insertion events (response, paragraph bridging pages 17-18). This is misleading, as random insertions events are encompassed by the claim. The construct of claim 1 does not contain targeting segments homologous to a pre-determined location in a host genome.

Claim Rejections - 35 USC § 103

8. Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoder et al. (WO 92/01370) in view of Hashimoto et al. (Plant Sci., February 1999, Vol. 141, pages 175-181), Bayley et al. (Plant Mol. Biol., 1992, Vol. 18, pages 353-361), and Suter-Crazzolara et al. (Meth. Cell Biol., 1995, Vol. 50, pages 425-438).

The claims are broadly drawn towards a DNA construct for integration of a heterologous DNA segment into genomes within any type of cell, the DNA construct comprising termini disposed therebetween heterologous DNA segments comprising: a) a pair of DNA substrates for any transposase, between which comprise i) first and second cloning sites, between which lies a positive selection gene encoding a product that confers resistance to a positive selection agent that is deleterious to cells in which the DNA construct has not integrated and ii) a negative selection gene disposed between one of the DNA substrates for the transposase and one of the two cloning sites, but not between the two cloning sites, wherein the negative selection gene confers renders the cell susceptible to a negative selective agent, wherein cells in which the DNA construct has not integrated are not susceptible to the agent, and optionally b) a detectable marker gene inserted in the DNA construct such that upon excision of the DNA construct from a genome by the action of the transposase, the detectable gene product is no longer detectable.

Yoder et al. teach methods to introduce heterologous DNA into genomes, comprising use of transposon systems. DNA constructs are made that comprise substrate sites recognized by a transposase. DNA within these sites can be from any source and can include selection and marker genes. The substrate sites recognized by the transposase can be from a maize Ds element, which is recognized by the maize Ac transposase. Heterologous genes of interest are

included on the construct, and can be included within or outside of the transposase substrate sites. Any selection or marker genes can be used, including that encoding β-glucuronidase and herbicide resistance genes such as those conferring resistance to phosphinothricin or glyphosate. Any types promoters can be used to express the selection, marker, and heterologous genes, including constitutive and inducible promoters. The DNA construct can be introduced into plants by any means, including via Agrobacterium, in which case the DNA construct would be within borders of Agrobacterium tDNA of a T-DNA vector (pages 6-15, 24-39)

Yoder et al. do not teach the cytosine deaminase (coda) gene.

Hashimoto et al. teach the use of the cytosine deaminase gene as a negative selection marker in plants. The CaMV 35S promoter was used to transcribe the gene in plants. Hashimoto et al. teach that this single gene is sufficient to provide good negative selection in plant systems (pages 177-180).

Bayley et al. teach the use of the Cre-lox recombination system to excise a luciferase gene from the genome of a tobacco plant. Transgenic plants comprising the lox sites and the luciferase gene were crossed with transgenic plants encoding the Cre recombinase. The excision event removed the luciferase coding sequence while leaving intact the promoter that was transcribing it. Bayley et al. also assert that the strategy yields cells devoid of DNA markers that are no longer required (pages 356-358, 360).

Suter-Crazzolara et al. teach several detectable marker genes, including GUS (page 426-431).

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made to modify the method of introducing heterologous genes into

genomes of Yoder et al. by using any other selection marker genes, such as the cytosine deaminase gene taught by Hashimoto et al. One would have been motivated to do so, given assertion by Hashimoto et al. that this gene is a good for use in plant systems. It would have been obvious to place cloning sites anywhere outside of the transposase substrate sites in the construct of Yoder et al., including the termini of the construct, to facilitate introduction of the gene(s) of interest. It would also have been obvious to place polylinker sites within the transposase substrate sites, to facilitate insertion of further selection, marker, or other heterologous genes. It also would be have been obvious to further modify the DNA construct by inserting a detectable marker gene within the construct such that a transposase substrate site was in between the promoter and the marker coding sequence, following the strategy used by Bayley et al. One would have been motivated to do so, given the demonstration by Bayley et al. that this strategy provides another tool to one of ordinary skill in the art to monitor the excision event following the action of the transposase, and their assertion that the excision event yield cells devoid of unwanted DNA markers. It also would have been obvious to use any detectable marker gene other than luciferase, such as those taught by Suter-Crazzolara et al., including GUS, and would have depended on one's desired end.

Applicant traverses (in the paper filed December 9, 2004) the rejection under 35 U.S.C. 103(a) presented in the Office action mailed September 10, 2004. Applicant's arguments were considered to the extent that they apply to the rejection above. Applicant argues that Yoder et al. do not teach or suggest the use of more than one selectable marker or the use of a negative selection gene, and that the use of transposons in Hashimoto et al. is to study mutational events within the cytosine deaminase gene (response, page 20, 1st and 2nd full paragraphs. Applicant

argues that because Yoder et al. do not teach a negative selection gene and Hashimoto et al. do not teach the use of a negative selection gene in a transposon-based construct, there is no suggestion or motivation within these references to modify or combine their teachings (response, paragraph bridging pages 21-22). However, it is not necessary that a reference actually suggest changes or possible improvements that Applicant made. See *In re Sheckler*, 438 F.2d 999, 1001; 168 USPQ 716, 717 (CCPA 1971). The ordinarily skilled artisan is presumed to know more about the art than only what is disclosed in the applied references, and has knowledge apart from the content of the references. *In re Bode*, 550 F.2d 656, 660, 193 USPQ 12, 16 (CCPA 1977); *In re Jacoby*, 309 F.2d 513, 516, 135 USPQ 317, 319 (CCPA 1962). Conclusions of obviousness can then be drawn "from common knowledge and common sense of the person of ordinary skill in the art without any specific hint or suggestion in a particular reference. *In re Bozek*, 416 F.2d 1385, 1390, 163 USPQ 545, 549 (CCPA 1969). Any selection marker genes can be used with the method taught by Yoder et al., and Hashimoto et al. teach that the cytosine deaminase gene is a good negative selective marker to use in plant systems.

9. Claims 29-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yoder et al. in view of Hashimoto et al., Bayley et al., and Suter-Crazzolara et al. as applied to claims 1-23 above, and further in view of Walden et al. (Plant Mol. Biol., 1994, Vol. 26, pages 1521-1528).

The claims are broadly towards a method for activation tagging of a plant genome to create variants displaying a desired phenotype.

Yoder et al. in view of Hashimoto et al., Bayley et al., and Suter-Crazzolara et al. teach DNA constructs for integration of DNA segments into cell genomes, as discussed above.

Yoder et al. in view of Hashimoto et al., Bayley et al., and Suter-Crazzolara et al. do not teach activation tagging.

Walden et al. teach a method for activation tagging of plant genomes, using a vector comprising promoter enhancer sequences to activate expression of genes in the genome, thereby producing mutants. The plants can be selected for a desired phenotype. Walden et al. demonstrate selection of plants having the ability to grow in the absence of auxin or cytokinin, or in the presence of an inhibitor of polyamine biosynthesis. Walden et al. also discuss advantages of activation tagging, such as isolation of genes involved in specific processes, and selection of specific mutations.

It would have been obvious and within the scope of one of ordinary skill in the art to further modify the DNA constructs taught by Yoder et al. in view of Hashimoto et al., Bayley et al., and Suter-Crazzolara et al. by inserting promoter enhancer sequences taught by Walden et al. It would have been obvious that doing so would have enabled use of the DNA construct in activation tagging of plant genomes. One would have been motivated to use the DNA construct for activation tagging, as Walden et al. teach that activation tagging can be used to select for desired phenotypes and isolate genes involved in specific processes.

10. Claims 1-32 remain rejected.

Contact Information

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. The fax phone numbers for the organization where this application or proceeding is assigned are 571-

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March 2, 2005

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